

Cervix uterine Cancer with Axillary and Neck Lymph Node Metastasis: An Unusual Finding

Alice Wendpanga Sorgho^{1*}, C. El Alouani¹, M Khouchani¹, S.I.R Soulama¹, F.E. Hazmiri², A. Ismail², H. Rais², H. Fennane³, Y. Msougar³

¹Department of Radiotherapy and Oncology, MOHAMMED VI University Hospital of Marrakech, Morocco

²Department of Pathology, MOHAMMED VI University Hospital of Marrakech, Morocco

³Department of thoracic surgery MOHAMMED VI University Hospital of Marrakech, Morocco

DOI: [10.36347/sjams.2023.v11i10.012](https://doi.org/10.36347/sjams.2023.v11i10.012)

| Received: 05.09.2023 | Accepted: 12.10.2023 | Published: 27.10.2023

*Corresponding author: Alice Wendpanga Sorgho

Department of Radiotherapy and Oncology, MOHAMMED VI University Hospital of Marrakech, Morocco

Abstract

Case Report

Background: Cervix uterii cancer is the fourth most common female malignancy. It commonly spreads by direct extension or lymphatic dissemination within the pelvis into the regional lymph nodes. Distant lymph node metastasis remains exceptional. To our knowledge, synchronous cervical and axillary lymph node metastasis from cervix cancer have never been reported. Here we report a case of cervical and axillary lymph node metastasis from cervix uterii cancer.

Case presentation: A 51-year-old woman diagnosed with cervix uterii cancer and treated with concomitant chemoradiotherapy, presented 8 months after the initial diagnosis multiple round masses located at the left side of her neck. F-18 FDG PET/CT revealed pathological axillary and neck lymph nodes. Histopathology and immunohistochemistry confirmed the metastatic nature of the lymph nodes. The patient underwent lymph node dissection before undergoing chemotherapy, followed by radiotherapy to the affected cervical and axillary lymph nodes.

Conclusions: Metastases from the uterine cervix to the neck lymph nodes are extremely uncommon. Lymphatic drainage and the lymph node jump phenomenon can explain the possible mode of cervical cancer tumor cell spread to the neck area. The mechanism of axillary lymph node metastasis from cervix uterii cancer can be explained by the communication between neck lymph nodes and axillary lymph nodes due to the alteration of the centripetal flow causing a retrograde spread. Distant lymph node metastasis in cervix uterii cancer are associated with a poor prognosis.

Keywords: cervix uterii cancer, neck lymph node metastasis, axillary lymph node metastasis, PET/CT, histopathology, immunohistochemistry, chemotherapy, radiotherapy.

Copyright © 2023 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

BACKGROUND

Cervix uterii cancer is the fourth most commonly diagnosed cancer among women [1]. Cervix uterii cancer commonly spreads by direct extension or lymphatic dissemination within the pelvis into the regional lymph nodes [2]. In cervical cancer, the progression of lymph node (LN) metastasis is gradual and begins from the nodes on the pelvic sidewall to the common iliac and then the para-aortic group [3]. The most commonly involved zone is the obturator area followed by the internal iliac and external iliac areas [3]. However, due to the improvement of treatment and increased survival, different metastatic sites have been reported. Nevertheless, distant lymph node metastasis remain exceptional [4]. To our knowledge, isolated cervical and axillary lymph node metastasis from cervix cancer have never been reported. Here, we report a case with those unusual locations of cervix cancer metastasis.

CASE PRESENTATION

A 51-year-old woman presented to the Gynecology department for management of abnormal vaginal bleeding of 4 months duration. Per-speculum examination showed a cervical ill defined borders growth with extension to the upper part of vagina. On MRI, the tumour was classified as FIGO IIB. An excisional biopsy was done, it revealed an invasive poorly differentiated squamous cell carcinoma. The patient was then referred to the oncology department where an extension workup was performed. Cervical thoracic and abdominal CT scan didn't reveal any lymph node metastasis. The treatment consisted of radiotherapy of 46Gy in 23 fractions of 1.8Gy for 5 weeks concomitant with cisplatin-based chemotherapy 40 mg/m² each week during radiotherapy. Uterovaginal curi-therapy with 7 fractions of 7gy with a boost of 12 Gy in 2 fractions of 6gy was performed. What resulted in clinical

Citation: Alice Wendpanga Sorgho, S. El Alouani, M. Khouchani, F.E. Hazmiri, A. Ismail, H. Fennane, H. Rais, Y. Msougar, S I R Soulama. Cervix uterine Cancer with Axillary and Neck Lymph Node Metastasis: An Unusual Finding. Sch J App Med Sci, 2023 Oct 11(10): 1834-1839.

improvement and a good therapeutic response at pelvic MRI. Five months later, the patient presented for multiple infracentimetric round masses located predominantly at the left side of her neck (Figure 1). An ultrasound of the supraortic trunks was done which revealed multiple suspicious rounded hypoechoogenic carotid-jugular lymph nodes with irregular contours located in the left side of the neck (Figure 4). The largest one was measuring 10.2x 9 mm. An F-18 FDG PET/CT was performed to detect any other hidden lesion and to assess the malignant potential of the lymph nodes. The latter revealed an axillary lymph node cluster with FDG uptake, with a maximum standardized uptake (SUVmax) of 5.7 and (Figure 5) had shown an hypermetabolic focus in cervical lymph nodes with a maximum standardized uptake (SUV max) of 3,6 (Figure 2 et 3).

The therapeutic approach consisted of a surgical resection of the suspicious cervical and axillary lymph nodes followed by chemotherapy with carboplatin D1 and gemcitabine 1000mg/m² D1;D8 in 6 cures spaced 21 days apart. The patient underwent a cervical lymphadenectomy which resulted in the removal of a lymph node. The other lymph nodes couldn't be removed due to their closeness to the vascular and nerve structures. The histopathological examination indicated a lymph node parenchyma involved by a poorly differentiated carcinomatous proliferation (Figures 4) compatible with a pathological nature of the lymph nodes. Immunohistochemical analysis showed positive nuclear staining for P63 antibody and positive nuclear and cytoplasmic staining for P16 antibody thus confirming the cervix uterii origin (Figures 5). Besides, an axillary lymph node dissection was performed. Twenty lymph nodes were dissected. On histopathological examination, 10 lymph nodes showed an infiltration by islands and cords of malignant carcinomatous process with some squamous features. Immunohistochemically, the tumor cells were also reactive with P63 and P16 antibodies (Figures 5) this confirming the metastatic nature of the axillary lymph node. Furthermore, neither echomammography or oropharynx endoscopy have shown abnormalities or suspicious lesions. Besides, a cervical thoracic and abdominal CT scan was negative for liver and lung metastasis. The patient subsequently received radiotherapy with 2 fractions of 30 GY in the left cervical area and 2 fractions of 27 GY in the axillary area. Finally she was put under surveillance. At present she has no signs of progression or recurrence with a clinical examination without any particularity with a normal pet scan and thoraco-abdomino-pelvic CT scan in a 2-year follow-up.



Figure 1: Pictures of left cervical adénopathies

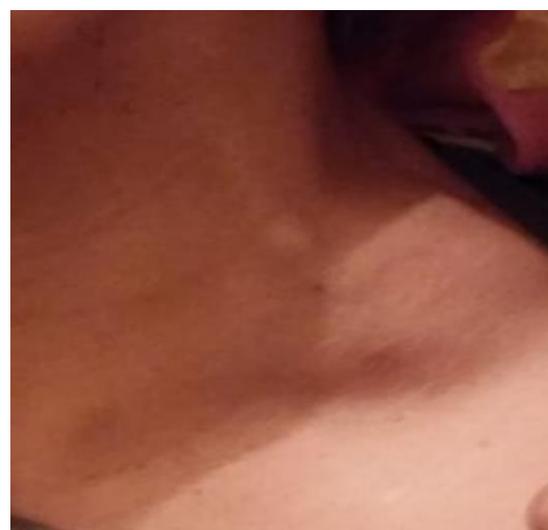


Figure 2: 18FDG PET/CT, transaxial views Demonstrated an hypermétabolique focus in axillary Lymph nodes (SUV max 5,7, red arrow)

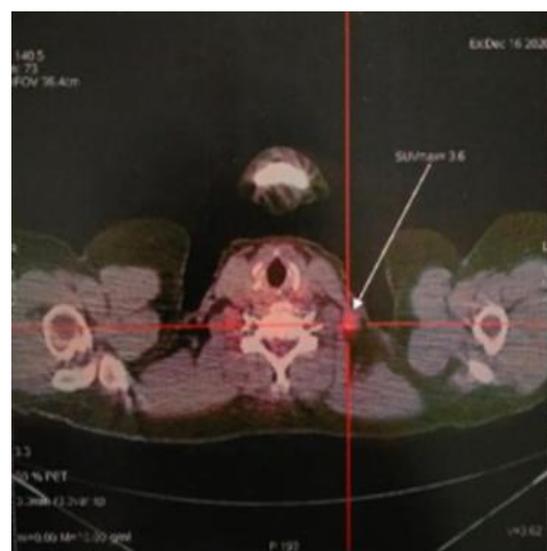


Figure 3: ultrasound of the supraortic trunks showing Multiple suspicious rounded hypoéchoogenic carotid-jugular Lymph nodes with irrégular contours

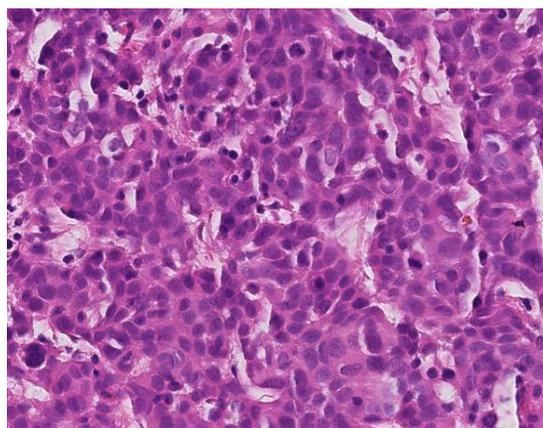


Figure 4 : lymph node parenchyma main volved by a poorly differentiated carcinomatous proliferation arranged in sheets, cords

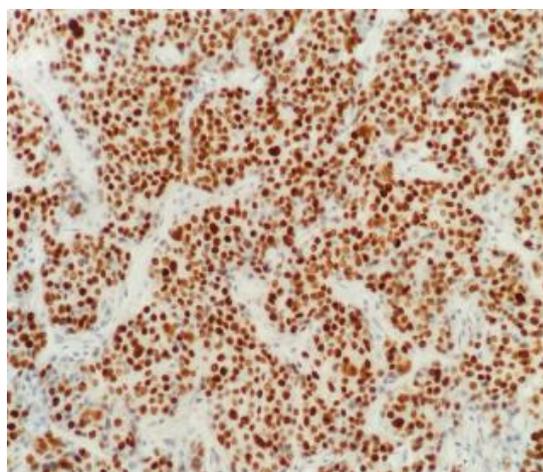


Figure 5: immunohistochemical staining for p63 showing Positive nuclear staining in the metastatic cells of the neck lymph node (HE, magnification X200)

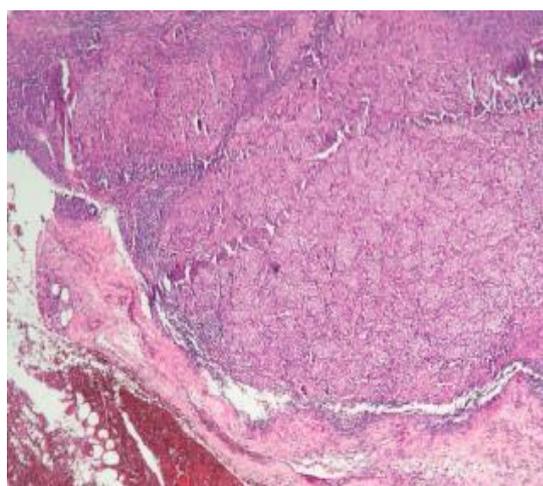


Figure 6: Carcinomatous cells with nuclei displaying anisocaryosis, irregular contours, abnormal mitosis and abundant eosinophilic cytoplasm (H&E, magnification X100)

DISCUSSION

In terms of both incidence and mortality, cervix uterii cancer occupies the fourth position in female [5]. It is well known that carcinoma of cervix exhibits a low incidence of distant metastases and more often spreads locally by direct extension [6] in a predictable pattern involving the endometrium superiorly and the upper vaginal wall inferiorly [7]. The tumor may spread laterally to the pelvic sidewall, anteriorly to the bladder base, or posteriorly to the rectum, starting from the parametrium [7]. The lymphatic drainage from the cervix is via three main groups of pelvic lymph nodes, including the internal and external iliac and the obturator lymph nodes. The tumour can reach the para-aortic group of lymph nodes, which is the most common extrapelvic site of lymphatic tumour spread, either directly through the posterior cervical trunk or via the subaortic and sacral lymph nodes. Efferent flow from the para-aortic lymph nodes is to the thoracic duct, which gives off some branches to the scalene or supraclavicular nodes, which explains the report of involvement of this group of lymph nodes.⁵ Extension via the cervical stroma or lymphovascular space invasion causes parametrial involvement [7]. To date, two forms of distant metastasis have been identified: lymph node and organ metastasis [5]. Lymphatic drainage can explain the possible mode of cervical cancer tumor cell spread to the neck area [8]. Lymphatic embolization of regional lymph nodes occurs when the lymphatic spaces which are present within 1-2mm of the basement membrane are involved by tumor cells especially with large volume tumors [9]. The lymphatic spread follows a constant course [10], starting by paracervical, hypogastric, obturator and external iliac group, then moving to sacral, common iliac, then aortic group, before extension beyond the pelvis from the abdominal para-aortic lymph nodes to the cisterna chyli and then to the thoracic duct which communicates with the systemic venous system in the neck at the junction of the left subclavian and internal jugular vein [6,10,11]. The thoracic duct incorporates the scalene lymph nodes into the efferent flow by arching above the clavicle and then empties into the venous system[11].

Neck lymph node metastasis from uterine cervix cancer are extremely uncommon [12]. Henriksen E. reported that the incidence of supraclavicular lymph node metastasis from cervix uterii cancer was 0.1% among treated patients and 1.5% among patients who haven't receive any treatment [12]. Ketcham and associates found that only 6 of 68 patients with cervix uterii cancer had scalene node metastases with only 2 patients having a palpable node [13]. The axillary lymph nodes are situated outside this path of pelvic drainage and receive their afferent flow from the upper limbs and chest wall. Therefore, axillary lymph nodes are extremely unlikely to be involved by a metastatic process from the pelvis or the lower abdominal region. In a chinese study of 123 patients, only 3 (2.4%) had axillary lymph node metastasis [14]. The mechanism of ALNM

from distant primary carcinoma is unclear [15] and may be explained by the communication between the cervical and axillary lymphatics [16]. That physiologic flow is centripetal, ending in the jugulosubclavian junction. [15,16]. The occurrence of metastasis in axillary lymph nodes is immensely rare due to this centripetal flow [16]. However, certain mechanism as the loss of the valvular competence of the lymphatic vessels or lymphatic blockade can cause the alteration of the centripetal flow leading to a retrograde spread of the lymphatic flow [15,16]. This retrograde flow spreads through the transverse cervical lymph node to the supraclavicular region and can finally end in the axillary lymph nodes leading to metastasis [16]. Computed tomography (CT), magnetic resonance imaging (MRI), lymphadenectomy, and lymphangiogram are all used to detect lymph node status [17]. For the clinical assessment of invasive cervical cancer, In our case, it was a FIGO IIB cervical cancer which metastasized directly into the extra pelvic lymph nodes without pelvic lymph node involvement. this can be explained by the lymph node relay skipping phenomenon. CT and MRI are the preferred instruments [17]. Positron emission tomography (PET) has shown superior sensitivity and specificity compared to CT or MRI in the detection of extra-pelvic metastases, including LNs.

It is considered the most effective non-invasive diagnostic imaging method to detect tumor metastases or recurrence of Known cervical uterine cancer [11,17]. The diagnosis of cervical cancer metastasis is essentially based on Histopathology [18]. However, morphology alone can not distinguish a cervical squamous cell carcinoma from squamous cell carcinomas of other anatomic sites, including the head and neck [12]. Thus, the use of immunohistochemistry is imperative for confirmation [19]. Overexpression of p16 is consistently observed in HPV-related cancers and is used as a marker for predicting the HPV status in the head and neck squamous cell carcinoma (SCC) and cervix uterii SCC [20]. HPV-positive cervical nodal disease draws attention first on the oropharynx HPV related cancers when no previous history of a primary tumor is noted [21]. In our case, the clinical history was marked by the prior cervix uterii cancer. In addition physical examination did not reveal any oropharyngeal lesion and positron emission tomography/computed tomography (PET/CT) has not detected any metabolic activity from the sites commonly involved in oropharyngeal HPV-related cancers (base of the tongue, tonsils and salivary glands) [12] which leads us to confirm the cervical origin of the lymph node metastasis. Breast cancer is the most common origin of axillary lymph node metastasis (ALNM) [11]. Involvement of axillary lymph nodes from cancer other than breast is extremely rare. Only a few cases of ALNM from cervical cancer have been reported [11]. P63, a useful marker of squamous neoplasms within the cervix, is of value in confirming that a poorly differentiated carcinoma is squamous in

type and when used in combination with P16, strongly points towards a cervix uterii origin [22]. Lymph node metastasis is one of the most predictive factor for recurrence and death [3]. The prognosis of metastatic cervical cancer is very bad. The median survival period of metastatic cervical cancer is 8 to 13 months with a 5-years survival rate of 16.5 %, compared to 91.5 % for localized cervical cancer [5].

The occurrence of nodal metastasis appear to be correlated to deep stromal invasion, parametrial involvement, lymphovascular space invasion and age [3]. Cervix uterii cancer patients with early-stage and locally advanced cancer can receive traditional therapies such as surgery, chemotherapy, or radiotherapy [17]. Concurrent Chemoradiotherapy seems to be the best therapeutic option for cervix uterii cancer with lymph node metastasis as it is well-tolerated and efficient [17]. Chemotherapy is indicated for metastatic forms of cervical cancer; it involves dual therapy with a platinum salt (level of evidence B1). Several cytotoxics have shown equivalent efficacy in combination with cisplatin: paclitaxel, topotecan, vinorelbine and gemcitabine. If possible, it is combined with other treatments such as surgery or radiotherapy, to achieve a curative effect aimed at eliminating cancer cells once and for all, for a lasting cure[23,24]. Carboplatin combined with gencitabine was administered after lymphadenectomy and finally radiotherapy to the affected lymph node sites in our case. This was followed by a good response with disappearance of all the above-mentioned metastases in our case. However, the patients with metastatic lymphadenopathy still have a poor outcome with a 5-year survival rate of 16.5% compared to 91.5% for localized cervical cancer [17].

CONCLUSION

Distant lymph node metastasis has become a more prevalent manifestation of recurrent cervical cancer as more recent improved treatment has emerged [12]. The manifestation of lymph node metastasis in patients with cervix carcinoma is associated with high tumor burden and poor prognosis [8]. Despite their rarity, distant LN metastases from cervical cancer should be investigated in patients with cervical uterine cancer by careful clinical examination of lymph node areas and adequate complementary imaging examinations. A biopsy with histopathological examination must be performed if metastasis is suspected. Appropriate management of lymph node recurrence leads to good control and improved survival.

Abbreviations:

LN: lymph node, CT: computed tomography, MRI: magnetic resonance imaging, F-18 FDG: fluorodeoxyglucose, PET: Positron Emission Tomography, SUVmax: Maximum Standardized Uptake Value, HE: Hematoxylin Eosin, HPV: Human Papilloma

Virus, SCC: Squamous cell carcinoma, ALNM: Axillary lymph node metastasis

Authors' contributions

FEH wrote the article and made substantial contributions to conception and design of the article; AI, YAB, HF, YM, SEA, MK and HR made critical assessment of the article; All authors have been involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Consent for publication

A written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Ethics approval and consent to participate

Not applicable.

Funding

The authors received no specific funding for this study.

REFERENCES

- Cohen, P. A., Jhingran, A., Oaknin, A., & Denny, L. (2019). Cervical cancer. *Lancet* (London, England), 393(10167), 169–182. [https://doi.org/10.1016/S0140-6736\(18\)32470-X](https://doi.org/10.1016/S0140-6736(18)32470-X)
- Manoharan, M., Satyanarayana, D. & Jeyarajah, A.R. Cervical lymphadenopathy – an unusual presentation of carcinoma of the cervix: a case report. *J Med Case Reports* 2, 252 (2008). <https://doi.org/10.1186/1752-1947-2-252>
- Huang, Bx., Fang, F. Progress in the Study of Lymph Node Metastasis in Early-stage Cervical Cancer. *CURR MED SCI* 38, 567–574 (2018). <https://doi.org/10.1007/s11596-018-1915-0>
- Tunio, M. A., Al Asiri, M., Mohamed, R., & Al-Dandan, S. (2013). Supraclavicular lymphadenopathy: initial manifestation of metastasis in carcinoma of cervix. *Case reports in obstetrics and gynecology*, 2013, 409196. <https://doi.org/10.1155/2013/409196>
- Yin, Z., Tang, H., Li, L., Ni, J., Yuan, S., Lou, H., & Chen, M. (2019). Impact of sites versus number of metastases on survival of patients with organ metastasis from newly diagnosed cervical cancer. *Cancer management and research*, 11, 7759–7766. <https://doi.org/10.2147/CMAR.S203037>
- Chawhan, S. M., Dani, A. A., Meshram, S. A., Randale, A. A., & Kumbhalkar, D. T. (2015). Metastases of squamous cell carcinoma of uterine cervix to duodenum: a case report. *Journal of clinical and diagnostic research : JCDR*, 9(1), ED03–ED4. <https://doi.org/10.7860/JCDR/2015/11428.5385>
- Maniar, K, Wei, J, *Glob. libr. women's med.*, (ISSN: 1756-2228) 2017; DOI 10.3843/GLOWM.10230
- Diddle A. W. (1972). Carcinoma of the cervix uteri with metastases to the neck. *Cancer*, 29(2), 453–455. [https://doi.org/10.1002/1097-0142\(197202\)29:2<453::aid-cnrcr2820290230>3.0.co;2-7](https://doi.org/10.1002/1097-0142(197202)29:2<453::aid-cnrcr2820290230>3.0.co;2-7)
- S.W. Aziz, M.H. Aziz Cervical Cancer Metastasis Introduction to Cancer Metastasis <http://dx.doi.org/10.1016/B978-0-12-804003-4.00005-0> Copyright © 2017 Elsevier Inc. All rights reserved.
- Erle Henriksen, The lymphatic spread of carcinoma of the cervix and of the body of the uterus: A study of 420 necropsies, *American Journal of Obstetrics and Gynecology*, Volume 58, Issue 5, 1949, Pages 924-942, ISSN 0002-9378, [https://doi.org/10.1016/0002-9378\(49\)90200-8](https://doi.org/10.1016/0002-9378(49)90200-8).
- Kang S. (2016). Unsuspected axillary lymph node metastasis of nasopharyngeal and cervical cancer on 18FDG PET/CT: a case report. *Nuclear medicine review. Central & Eastern Europe*, 19(B), 20–21. <https://doi.org/10.5603/NMR.2016.0032>
- López, F., Rodrigo, J. P., Silver, C. E., Haigentz, M., Jr, Bishop, J. A., Strojjan, P., Hartl, D. M., Bradley, P. J., Mendenhall, W. M., Suárez, C., Takes, R. P., Hamoir, M., Robbins, K. T., Shaha, A. R., Werner, J. A., Rinaldo, A., & Ferlito, A. (2016). Cervical lymph node metastases from remote primary tumor sites. *Head & neck*, 38 Suppl 1(Suppl 1), E2374–E2385. <https://doi.org/10.1002/hed.24344>
- Kang S. (2016). Unsuspected axillary lymph node metastasis of nasopharyngeal and cervical cancer on 18FDG PET/CT: a case report. *Nuclear medicine review. Central & Eastern Europe*, 19(B), 20–21. <https://doi.org/10.5603/NMR.2016.0032>
- Lou, H. M., & Li, Q. (2007). Ai zheng = Aizheng = Chinese journal of cancer, 26(11), 1248–1251.
- Riquet, M., Le Pimpec-Barthes, F., & Danel, C. (1998). Axillary lymph node metastases from bronchogenic carcinoma. *The Annals of thoracic surgery*, 66(3), 920–922. [https://doi.org/10.1016/s0003-4975\(98\)00556-6](https://doi.org/10.1016/s0003-4975(98)00556-6)
- Murat Ozdemir, Ege Universitesi Tip Fak, Hastanesi, Genel Cerrahi. (2015). Medullary Carcinoma of the Thyroid with Axillary Metastasis: A Case Report *Int Surg* 2015; 100: 390–393. DOI: 10.9738/INTSURG-D-13-00274.1
- Li, H., Wu, X., & Cheng, X. (2016). Advances in diagnosis and treatment of metastatic cervical

- cancer. *Journal of gynecologic oncology*, 27(4), e43. <https://doi.org/10.3802/jgo.2016.27.e43>
18. Vinh-Hung V, Bourgain C, Vlastos G, Cserni G, De Ridder M, Storme G, Vlastos AT. Prognostic value of histopathology and trends in cervical cancer: a SEER population study. *BMC Cancer*. 2007 Aug 23; 7: 164. doi: 10.1186/1471-2407-7-164. PMID: 17718897; PMCID: PMC1994954.
 19. Chih-Wei Wang, and al. Usefulness of p16 for Differentiating Primary Pulmonary Squamous Cell Carcinoma From Cervical Squamous Cell Carcinoma Metastatic to the Lung, *American Journal of Clinical Pathology*, Volume 131, Issue 5, May 2009, Pages 715–722, <https://doi.org/10.1309/AJCPTPBC6V5KUITM>
 20. Lin, S., Zhang, X., Li, X., Qin, C., Zhang, L., Lu, J., Chen, Q., Jin, J., Wang, T., Wang, F., & Zang, S. (2020). Detection of human papillomavirus distinguishes second primary tumors from lung metastases in patients with squamous cell carcinoma of the cervix. *Thoracic cancer*, 11(8), 2297–2305. <https://doi.org/10.1111/1759-7714.13544>
 21. Marc R. Rohrbach, Christopher J. Britt, Michael Schwalbe, Aaron M. Wieland, Gregory K. Hartig, p16 Immunohistochemistry Is a Useful Diagnostic Adjunct in Cases of Metastatic Cervical Carcinoma of Unknown Origin, *Journal of Oral and Maxillofacial Surgery*, Volume 75, Issue 3, 2017, Pages 525-529, ISSN 0278-2391, <https://doi.org/10.1016/j.joms.2016.08.029>
 22. Houghton, O., & McCluggage, W. G. (2009). The expression and diagnostic utility of p63 in the female genital tract. *Advances in anatomic pathology*, 16(5), 316–321. <https://doi.org/10.1097/PAP.0b013e3181b507c6>
 23. Institut de radiothérapie et de radiochirurgie h. Hartmann, Le traitement de la récurrence du cancer du col de l'utérus, 21juin 2021
 24. Cancers du col utérin, Référentiels de l'AP-HP-- Juin 2016